Metabolomics for Developing Markers of Chemical Exposure and Distinguishing Toxicity Pathways

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Metabolomics involves the application of advanced analytical and statistical tools to profile changes in levels of endogenous metabolites in tissues and biofluids resulting from disease onset, stress, or chemical exposure. Nuclear magnetic resonance (NMR) spectroscopy–based metabolomics has proven useful in mammalian systems for distinguishing between sites and mechanisms of toxicity for tissue-specific toxins. Metabolomics has been characterized as the true measure of metabolic outcomes suggested by changes in gene and protein expression; as such, metabolomics provides a connection between these molecular endpoints and whole organism responses. Although used mostly in mammalian studies, metabolomics is now finding utility in a wide variety of other organisms, including aquatic species.

We have developed a research program in metabolomics that involves numerous partners across EPA, other Federal labs, academia, and the private sector. Our goals are to (1) develop metabolite-based markers that can be used by EPA in chemical exposure assessments and (2) develop and test hypotheses about toxicity pathways for risk assessments. We are focusing this program on ecologically relevant species—in particular, small fish toxicological models.

For example, to better understand the mode of action of endocrine-disrupting chemicals (EDCs) in small fish (fathead minnow, zebrafish), we are conducting metabolomic analyses with multiple tissues (brain, blood, liver, and gonad) and urine. Initial metabolomic studies were focused on collection of baseline data for actively spawning male and female fathead minnows. Subsequent work is focusing on animals exposed to potent EDCs, such as the steroid 17α-ethinylestradiol (EE2). We are developing hypotheses about which tissue- and biofluid-specific metabolite changes will be definitively related to exposure based on the current understanding of modes of action for these chemicals. Results will allow testing of these hypotheses to refine understanding of activity and will help ensure that molecular markers of EDC exposure—another outcome of this research—are meaningful. While certain metabolites are being specifically targeted in these studies, we will also discern changes in the complete metabolic profile using NMR spectroscopic data with statistical approaches that allow capturing subtle changes in less-abundant metabolites. These data will be integrated with genomic, proteomic, and whole organism data from untreated fish and those exposed to known EDCs.

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